

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/008114

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/54 C07K14/55 C12N15/62 C12N15/861 A61K48/00  
A61K38/19

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 158 198 A (TAKEDA CHEMICAL INDUSTRIES LTD) 16 October 1985 (1985-10-16)  the whole document	1,2,5-7, 17-19, 29-31, 34-36
X	ROCK F ET AL: "OVEREXPRESSION AND STRUCTURE-FUNCTION ANALYSIS OF A BIOENGINEERED IL-2/IL-6 CHIMERIC LYMPHOKINE" PROTEIN ENGINEERING, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 5, no. 6, September 1992 (1992-09), pages 583-591, XP000983961 ISSN: 0269-2139 abstract  ----- -/--	1,2,5-7, 17-19, 29-31, 34-36

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

2 March 2005

Date of mailing of the international search report

31.03.05

Name and mailing address of the ISA

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 225 579 A (SEARLE & CO) 16 June 1987 (1987-06-16)  page 8; claim 8	1,2,5-7, 17-19, 29-31, 34-36
X	EP 0 288 809 A (HOECHST AG) 2 November 1988 (1988-11-02) the whole document	1-5
X	EP 0 816 510 A (TORAY RESEARCH CENTER INC ; TORAY INDUSTRIES (JP)) 7 January 1998 (1998-01-07) the whole document	1-5
X	WO 94/21792 A (VIAGENE INC) 29 September 1994 (1994-09-29)	1-9, 15-20, 22, 26-31, 34-36, 38,40 19-23
Y	pages 10,13,29; claims 1,9,11,17	
Y	WO 98/40498 A (SULLIVAN DANIEL M ; US ARMY (US); ANGLADE EDDY (US); CSAKY KARL G (US)) 17 September 1998 (1998-09-17) figure 1	19-21
Y	WO 99/36440 A (HAWKINS ROBERT EDWARD ; UNIV BRISTOL (GB); WHITTINGTON HAYLEY ANN (GB)) 22 July 1999 (1999-07-22) claim 27	19-21
Y	WO 98/08947 A (US HEALTH) 5 March 1998 (1998-03-05)  pages 16,19,44	1-11, 15-38, 40,41
Y	KAUFMANN A.M. ET AL: "Comparison of cytokines and CD80 for enhancement of immunogenicity of cervical cancer cells" IMMUNOBIOLOGY, vol. 202, no. 4, October 2000 (2000-10), pages 339-352, XP009040509 GERMANY abstract	1-9, 15-38, 40,41
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KONDO M ET AL.: "Enhancement of Interleukin-2 induced lymphokine-activated killer activity by Interleukin-7 against autologous human renal cell carcinoma" ONCOLOGY, vol. 55, no. 6, November 1998 (1998-11), pages 588-593, XP009040510 SWITZERLAND abstract	1-9, 15-38, 40,41
Y	JU D W ET AL: "Adenovirus-mediated combined suicide gene and interleukin-2 gene therapy for the treatment of established tumor and induction of antitumor immunity." JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY. 1998, vol. 124, no. 12, 1998, pages 683-689, XP002307305 ISSN: 0171-5216 abstract	22,23
Y	US 6 552 005 B1 (MILLER C RYAN ET AL) 22 April 2003 (2003-04-22) the whole document	23
Y	WO 93/20849 A (UNIV TEXAS) 28 October 1993 (1993-10-28) cited in the application the whole document	10,11
Y	WO 99/60128 A (LEMBACH KENNETH J ; SHANAFELT ARMEN B (US); JESMOK GARY (US); BAYER AG) 25 November 1999 (1999-11-25) cited in the application the whole document	10,11
Y	SHANAFELT ARMEN B ET AL: "A T-cell-selective interleukin 2 mutein exhibits potent antitumor activity and is well tolerated in vivo" NATURE BIOTECHNOLOGY, vol. 18, no. 11, November 2000 (2000-11), pages 1197-1202, XP002307306 ISSN: 1087-0156 cited in the application the whole document	10,11
X	WO 02/102404 A (INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE; COMMONWEALTH SCIENTIFIC) 27 December 2002 (2002-12-27) page 24, lines 27,28; sequences 6,8,10	1-9
Y		10-41
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WIGGINTON JON M ET AL: "Synergistic engagement of an ineffective endogenous anti-tumor immune response and induction of IFN-gamma and Fas-ligand-dependent tumor eradication by combined administration of IL-18 and IL-2" JOURNAL OF IMMUNOLOGY, vol. 169, no. 8, 15 October 2002 (2002-10-15), pages 4467-4474, XP002319786 ISSN: 0022-1767 abstract	8-41
Y	SON YOUNG-IK ET AL: "Interleukin-18 (IL-18) synergizes with IL-2 to enhance cytotoxicity, interferon-gamma production, and expansion of natural killer cells" CANCER RESEARCH, vol. 61, no. 3, 1 February 2001 (2001-02-01), pages 884-888, XP002319787 ISSN: 0008-5472 abstract page 887, last paragraph	8-41
Y	WO 01/93898 A (SMITHKLINE BEECHAM CORPORATION; ESSER, KLAUS, M; ROSENBERG, MARTIN; TA) 13 December 2001 (2001-12-13) claims 7-9; example 5	8-41
Y	WO 03/035105 A (CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER; GALIPEAU, JACQUES; STAGG,) 1 May 2003 (2003-05-01) page 13; claims 1,2,20	8-41
X	WO 01/68896 A (THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY) 20 September 2001 (2001-09-20) cited in the application	1-6
Y	page 24, lines 14-18 page 7, line 6; claims 27-32	8-41
Y	WO 01/10912 A (LEXIGEN PHARMACEUTICALS CORP) 15 February 2001 (2001-02-15) page 9, lines 8-12	18,19
Y	WO 02/101049 A (ARES TRADING S.A) 19 December 2002 (2002-12-19) claim 4	12,13
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WANG Q ET AL: "Intratumoral IL-18 gene transfer improves therapeutic efficacy of antibody-targeted superantigen in established murine melanoma" GENE THERAPY, vol. 8, no. 7, April 2001 (2001-04), pages 542-550, XP002319788 ISSN: 0969-7128 page 548, right-hand column, paragraph 2 -----</p>	18,19

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2004/008114

## Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:  
1-41 as far as they relate to fusions of IL-2 with IL-7  
and fusions of IL-18 with IL-2
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

**This International Searching Authority found multiple (groups of) inventions in this international application, as follows:**

## Invention 1

claims 1-11,15-41 as far as they relate to any of the specific combinations of IL-2 with IL-7

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## Inventions 2-7

claims 1-11, 15-41 as far as they relate to any of the specific combinations of IL-2 with any of IL-15, IL-18, IL-21, IL-27, IL-31, or IFN $\gamma$

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## Invention 8

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-7

**Abstract**

## Invention 9

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-15

— — —

## Invention 10

claims 1-41  
as far as they relate to fusion proteins comprising IL-18

**Abstract**

## Invention 11

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-21

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## Invention 12

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-27

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### Invention 13

claims 1-11, and 15-41  
as far as they relate to fusion proteins comprising IL-31

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## Inventions 14-19

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

claims 1-11,15-41 as far as they relate to any of the  
specific combinations of IFNgamma with

- (8.1.) IL-15
- (8.2.) IL-18
- (8.3.) IL-21
- (8.4.) IL-27
- (8.5.) IL-31
- (8.6.) IL-7

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EP 1 700 000 A1



## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/008114

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**PCT/EP2004/008114**

100

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Information on patent family members

International Application No

PCT/EP2004/008114

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